Amendments to the Specification:

Please replace the paragraph beginning on page 3, line 1, with the following amended paragraph:

Therapeutic and diagnostic uses of nucleic acids that encode various inhibitors of apoptosis relating to a member of the IAP family have been described in the patent literature. See, for example, International Patent Applications No. WO 97/06255, WO 97/26331, and WO 97/32601. In particular, the uses of such genes and gene products are contemplated for the novel protein and its encoding nucleic acid ~~diseusssed~~ discussed below.

Please replace the paragraph beginning on page 14, line 4, with the following amended paragraph:

Survivin was found to be a small protein of 142 amino acids (~ 16.5 kDa) with no amino acid sequence homology to EPR-1, and designated Survivin for the presence of a BIR-homologous domain (Birnbaum, M.J. *et al.*, *J Virology* (1994) 68:2521-2528; Clem, R.J. *et al.*, *Mol Cell Biol* (1994) 14:5212-5222) found in IAP inhibitors of apoptosis (Duckett, C.S. *et al.*, EMBO J (1996) 15:2685-2694; Hay, B.A. *et al.*, Cell (1995) 83:1253-1262; Liston, P. *et al.*, Nature (1996) 379:349-353; Rothe, M. *et al.*, Cell (1995) 83:1243-1252; Roy, N. *et al.*, Cell (1995) 80:167-178). Based on overall sequence conservation, the absence of a carboxy terminus RING finger and the presence of a single, partially conserved, BIR domain, Survivin is the most distantly related member of the IAP family, sharing the highest degree of similarity with NAIP (Roy, N. *et al.*, Cell (1995) 80:167-178). Thus, unlike bcl-2 or other IAP ~~proetins~~ proteins, Survivin is undetectable in adult tissues, but becomes ~~prominetnly~~ prominently expressed in all the most common human cancers of lung, colon, breast, pancreas, and prostate, and in ~50% of high-grade non-Hodgkin's lymphomas, in vivo. Additionally, unlike other IAP proteins (Deveraux, Q. *et al.*, Nature (1997) 388:300-304), Survivin does not bind caspases in a cell-free system (Roy, N. *et al.*, Blood (1997) 595:2645.

Please replace the paragraph beginning on page 20, line 4, with the following amended paragraph:

As described below, members of the Survivin family of proteins can be used: 1) as a target to block Survivin mediated inhibition of cellular apoptosis, 2) to identify and isolate binding partners that bind Survivin, 3) in methods to identify agents that block the association of Survivin with a Survivin binding partner, 4) as a target to assay for Survivin mediated inhibition of cellular apoptosis, 5) as an agent to block cellular apoptosis, administered alone or as part of a combination therapy, 6) as a binding partner in an assay to quantitate circulating levels of anti-Survivin antibodies, 7) as an antigen to elicit production of anti-Survivin antibodies that in turn can be used in an ~~an~~ assay to quantitate circulating levels of Survivin and or can be used for immunohistochemical purposes, and 8) as a therapeutic anti-cancer vaccine, or component of a polyvalent vaccine.

Please replace the paragraph beginning on page 22, line 7, as amended in the Preliminary Amendment of May 6, 2002, with the following amended paragraph:

As used herein, "stringent conditions" are conditions in which hybridization yields a clear and detectable sequence. Stringent conditions are those that (1) employ low ionic strength and high temperature for washing, for example, 0.015 M NaCl, 0.0015 M sodium ~~titrate~~ citrate, 0.1% SDS at 50°C; or (2) employ during hybridization a denaturing agent such as formamide, for example, 50% (vol/vol) formamide with 0.1% bovine serum albumin, 0.1% Ficoll, 0.1% polyvinylpyrrolidone, 50 mM sodium phosphate buffer at pH 6.5 with 750 mM NaCl, 75 mM sodium citrate at 42°C. Another example is use of 50% formamide, 5x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5x Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2x SSC and 0.1% SDS. A skilled artisan can readily determine and vary the stringency conditions appropriately to obtain a clear and detectable hybridization signal.

Please replace the paragraph beginning on page 37, line 11, with the following amended paragraph:

Inhibition of Survivin activity/expression can be used in combination with conventional chemotherapies. The timing for using a chemotherapeutic agent in combination with inhibiting Suvivin activity/expression depends upon chemotherapeutic agent used and the tumor cell type treated. Examples of chemotherapeutic agents that can be used in combination with agents the effect Survivin activity/expression, includes, but is not limited to alkylating agents, such as cyclophosphamide (CTX; cytoxan), chlorambucil (CHL; leukeran), cisplatin (CisP; platinol) busulfan (myleran), melphalan, carmustine (BCNU), streptozotocin, triethylenemelamine (TEM), mitomycin C, and the like alkylating agents; anti-metabolites, such as methotrexate (MTX), etoposide (VP16; vepesid) 6-mercaptopurine (6MP), ~~6-thioguanine~~ 6-thioguanine (6TG), cytarabine (Ara-C), 5-fluorouracil (5FU), dacarbazine (DTIC), and the like anti-metabolites; antibiotics, such as actinomycin D, doxorubicin (DXR; adriamycin), daunorubicin (daunomycin), bleomycin, mithramycin and the like antibiotics; alkaloids, such as vinca alkaloids such as vincristine (VCR), vinblastine, and the like; and other antitumor agents, such as taxol and taxol derivatives, the cytostatic agents glucocorticoids such as dexamethasone (DEX; decadron) and corticosteroids such as prednisone, nucleoside enzyme inhibitors such as hydroxyurea, amino acid depleting enzymes such as asparaginase, and the like diverse antitumor agents.

Please replace the paragraph beginning on page 39, line 18, with the following amended paragraph:

In addition to being a marker of tumor aggressiveness and treatment potential, Survivin expression can be used as a measurement of the effectiveness of anti-tumor therapy. In the Examples, it is shown that HL-60, a ~~promylocytic~~ promyelocytic cell line, had high levels of Survivin expression. Treatment of HL-60 cells with retenoic acid, and anti-cancer agent that acts by causing the ~~differention~~ differentiation of tumor cells, resulted in a reduction and elimination of Survivin expression. The reduction in expression correlated with the degree of differentiation,

the greater the differentiation, the lower the level of Survivin expression. Accordingly, Survivin expression can be used to measure the effectiveness of anti-tumor treatment: if Survivin expression decreases during treatment, the treatment protocol is effective and can be continued, whereas if Survivin expression remains unaltered, a different therapeutic regime or protocol needs to be performed.

Please replace the paragraph beginning on page 42, line 12, with the following amended paragraph:

Retroviral vectors, adenoviral vectors, adeno- associated viral vectors, or other viral vectors with the appropriate tropism for cells likely to be involved in apoptosis (for example, epithelial cells) may be used as a gene transfer delivery system for a therapeutic Survivin gene construct. Numerous vectors useful for this purpose are generally known (Miller, Human Gene Therapy 15-14, 1990; Friedman, Science 244:1275-1281, 1989; Eglitis and Anderson, BioTechniques 6:608-614, 1988; Tolstoshev and Anderson, current opinion in biotechnology 1:55-61, 1990; Sharp, The Lancet 337:1277-1278, 1991; Cornetta *et al.*, Nucleic Acid Research and Molecular Biology 36:311-322, 1987; Anderson, Science 226:401-409, 1984; Moen, blood Cells 17:407-416, 1991; Miller *et al.*, Biotechniques 7:980-990, 1989; Le Gal La Salle *et al.*, Science 259:988-990, 1993; and Johnson, Chest 107:77S-83S, 1995). Retroviral vectors are particularly well developed and have ~~ben~~ been used in clinical settings (Rosenberg *et al.*, N. Engl. J. Med 323:370, 1990; Anderson *et al.*, U.S. Patent No. 5,399,346).

Please replace the paragraph beginning on page 65, line 10, with the following amended paragraph:

Potential implications. The demonstrated role of Survivin as a negative predictive prognostic factor in these two embryologically different types of cancer iterates the potential use of this molecules a ~~dinnostic~~ diagnostic tool to monitor disease progression and response to the therapy. It can also be used for staging purposes and to identify populations of patients potentially susceptible to multi-drug resistance (groups with no remissions or incomplete

remissions). Also, Survivin derived primers easily designed from the complete sequence of the Survivin gene can be used as a screening tool to identify potential cases of cancer in which the Survivin gene has been deleted or mutated. These cases will be very important to identify because targeted inactivation of the Survivin gene would confer a favorable prognostic factor to cancer patients, removing a potential drug-resistance gene. Inactivating mutations in the Survivin gene can target the same key residues identified in our initial screening of Ala-based mutagenesis or result in an abortive or truncated protein for premature termination of translation.

Please replace the paragraph beginning on page 66, line 6, with the following amended paragraph:

Methods of ~~rthe~~ the use of peptide components in a monovalent or a polyvalent cancer immunotherapy-vaccine product are described by Nardi, N. *et al.*, *Mol. Med.* (1995) 1(5):563-567. Additional references that discuss the different cancer vaccine and cancer immunotherapies currently being used include: N.P. Restifo and M. Sznol "Cancer Vaccines," in DeVita's Cancer: Principles & Practice of Oncology 3023-3043 (Lippincott-Raven, Philadelphia; 1997); J. Galea-Lauri *et al.*, *Cancer Gene Ther.* (1996) 3(3): 202-214; D.C. Linehan *et al.*, *Ann. Surg. Oncol.* (1996) 3(2): 219-228; and J. Vieweg *et al.*, *Cancer Invest.* (1995) 13(2): 193-201.

Please replace the paragraph beginning on page 68, line 4, with the following amended paragraph:

For diagnostic uses, blood is drawn from patients, by well known techniques, who have known cancer loads or from patients suspected of having cancer. The blood sample is prepared by known techniques and is tested for binding with antibodies to Survivin that are prepared and, optionally, labeled, as discussed above. Such general antibody detection protocols and associated reagents are well established in the art. Other biological fluid samples such as semen, urine, or saliva can also be monitored for the presence of Survivin. This diagnostic technique ~~aso~~ also can be used to monitor disease progression and response to individualized therapies. This method offers a relatively non-invasive means of tracking cancer progression or regression.

Please replace the paragraph beginning on page 69, line 14, with the following amended paragraph:

Example ~~16~~ 18 **DETECTING SURVIVIN USING A DIRECT ELISA TEST**

Please replace the paragraph beginning on page 70, line 4, with the following amended paragraph:

Example ~~18~~ 19 **SURVIVIN FRAGMENTS, PEPTIDES AND SMALL MOLECULE ANTAGONISTS**

Please replace the paragraph beginning on page 71, line 15, with the following amended paragraph:

Example ~~19~~ 20 **THERAPEUTIC USES OF ANTISENSE SURVIVIN DNA**

Please replace the paragraph beginning on page 71, line 29, with the following amended paragraph:

Example ~~20~~ 21 **USE OF SURVIVIN AS A PROTECTIVE AGENT AGAINST APOPTOSIS**

Please replace the paragraph beginning on page 72, line 15, with the following amended paragraph:

The use of Survivin or allelic ~~varients~~ variants of Survivin in subjects to modulate or prevent apoptosis related cell death would be beneficial in treating or ameliorating the effects of a variety of apoptosis-related indications. These indications include, but are not limited to, dermatological effects of aging (*e.g.*, baldness that is caused by apoptosis of cells of hair follicle

cells), disorders and diseases such as immunosuppression, gastrointestinal perturbations (*e.g.*, damage of lining of the gut, ulcers, and radiation or chemotherapy induced damage), cardiovascular disorders, apoptosis related to reperfusion damage (*e.g.*, coronary artery obstruction, cerebral infarction, spinal/head trauma and concomitant severe paralysis, damage due to insults such as frostbite or burns, and any indication previously thought to be treatable by superoxide dismutase), rejection of tissue transplantation (*e.g.*, graft versus host disease), and Alzheimer's disease. The administration of Survivin also may be cytoprotective against chemotherapy or radiation-induced apoptosis.